Curis-Sponsored 1st Annual IRAK4 in Cancer Symposium Highlights IRAK4 as a Promising Therapeutic Target in Hematologic Cancers and Solid Tumors

Experts across academia and industry discussed IRAK4's biological and immunological roles in hematologic cancers and solid tumors and emerging developments in the therapeutic targeting of IRAK4.

Presentations highlighted IRAK4 activation by splicing mutations or upstream signaling as a key event driving progression of multiple cancer types and conferring sensitivity to investigational IRAK4 inhibitors such as emavusertib.

Curis, Inc. (NASDAQ: CRIS), a biotechnology company focused on the development of innovative therapeutics for the treatment of cancer, sponsored a successful 1st Annual IRAK4 in Cancer Symposium, held virtually on October 7, 2022, and hosted by Drs. Guillermo Garcia-Manero, Hagop Kantarjian, and Amit Verma.

Interleukin-1 receptor-associated kinase-4 (IRAK4) is a protein kinase belonging to the tyrosine-like kinase family. IRAK4 functions as a mediator of Toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling pathways and plays an important role in the innate immune response. Emerging evidence has associated oncogenic and spliceosome mutations in these pathways with increased activation of IRAK4 in multiple cancers, indicating the potential of targeting IRAK4 for therapeutic intervention.

Highlights of the 1st Annual IRAK4 in Cancer Symposium included:

Overview of IRAK4 Biology
Dr. Amit Verma (Montefiore; Albert Einstein College of Medicine) shared emerging research on two different mutations in messenger RNA (mRNA) splicing factors common in myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) that drive expression of a maximally active long-splicing isoform of IRAK4 termed IRAK4-L. IRAK4-L expression correlates with a worse prognosis but confers sensitivity to the IRAK4 inhibitor emavusertib (CA-4948).

Dr. Daniel Starczynowski (Cincinnati Children's Hospital Medical Center) further explored the mechanisms by which leukemia stem cells and progenitor cells utilize the IRAK4 pathway to drive pro-oncogenic changes and found that the maximally active IRAK4-L isoform is preferentially expressed in breast, colon, and lung cancers.

Dr. Ulrich Steidl (Montefiore; Albert Einstein College of Medicine) described how the analysis of pre-leukemic and leukemia stem cells reveals the importance of interleukin-1 receptor accessory protein (IL1RAP) in driving activation of the IRAK4 pathway in both AML and MDS.

Role of IRAK4 in Innate Immunity
Dr. Alan List (Precision BioSciences, Inc.) discussed the impact of the activation of TLR and NLRP3 inflammasome signaling pathways on hematopoiesis and inflammatory cytokine generation in lower-risk MDS (LR-MDS). LR-MDS and age-related clonal hematopoiesis disorders are promising targets for dual suppression by inhibitors of the TLR pathway, such as IRAK4 inhibitors, combined with inhibitors of the NLRP3 inflammasome.

IRAK4 in Hematologic Cancers
Dr. Guillermo Garcia-Manero (MD Anderson Cancer Center) presented promising clinical safety and efficacy data of the single-agent IRAK4 inhibitor emavusertib in heavily pretreated AML and high-risk MDS patients with spliceosome mutations (*U2AF1, SF3B1,* or *FLT3*).

Dr. Grzegorz Nowakowski (Mayo Clinic) gave an overview of the Bruton's Tyrosine Kinase (BTK) and TLR pathways that drive oncogenic activity in B cell malignancies and shared compelling research highlighting the clinical safety and activity of emavusertib as a single agent and in combination with a BTK inhibitor for non-Hodgkin's lymphoma.

Dr. Omar Abdel-Wahab (Memorial Sloan Kettering Cancer Center) found that inhibition of the CDC2-like kinase (CLK)/dual-specificity tyrosine phosphorylation-regulated kinase (DYRK) family impacts mRNA processing, such as intron retention, and overcomes resistance to venetoclax in preclinical AML models. A novel CLK inhibitor (CTX-712) is currently being assessed in a first-in-human phase 1 clinical trial. Furthermore, in addition to binding to IRAK4, emavusertib also binds to CLK/DYRK family kinases, suggesting the potential for additional mechanisms by which emavusertib may act.

IRAK4 in Solid Tumors

Dr. Kian-Huat Lim (Washington University School of Medicine) reviewed the potential of IRAK4 as a therapeutic target in pancreatic and colon cancer and shared compelling preclinical evidence that IRAK4 inhibition with emavusertib improved tumor responses in pancreatic cancer.

IRAK4 Therapeutic Strategies

Dr. Daniel Starczynowski (Cincinnati Children's Hospital Medical Center) presented data on the roles of the TLR/IRAK4 pathway in driving adaptive resistance to targeted therapies such as FLT3 inhibitors in AML. Dual inhibition targeting FLT3 and IRAK4 may be a promising strategy to overcome therapy resistance.

Dr. Robert Martell (Curis, Inc.) gave an overview of the clinical development of emavusertib and shared the preclinical and emerging positive clinical outcomes of IRAK4 kinase inhibition in hematologic malignancies. Clinical development of emavusertib has been directed by a growing understanding of the biology of its targets. Ongoing Curis clinical studies are assessing emavusertib in the relapsed/refractory setting as monotherapy in AML/MDS with specific mutations in *FLT3* or the spliceosome, as a combination therapy with either venetoclax or histone methylating agents in AML and MDS, and as a combination therapy with ibrutinib in B cell malignancies where the IRAK4 pathway is activated.

Key Summary

These compelling presentations captured the excitement among IRAK4 experts and provided valuable insights into understanding IRAK4's biology and therapeutic potential in cancer. IRAK4 activity has been implicated in the progression of multiple cancer types, including hematologic malignancies and solid tumors. Understanding the biology driving IRAK4 and the implications of IRAK4 signaling on innate immunity is key to harnessing its therapeutic potential. Notably, the IRAK4 inhibitor CA-4948 (emavusertib) has shown promise in multiple preclinical cancer models. It is currently being assessed in clinical trials as a monotherapy and combination therapy for AML, MDS, and B cell cancers.